# Scaling Basic Toxicokinetic Parameters from Rat to Man

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Scaling of the quantified dispositional parameters of xenobiotics from animals to man is of interest from the standpoint of toxicology (e.g., poisoning and risk assessment). Scaling is also important from the standpoint of therapeutics because it represents a strategy for predicting first-use-in-human doses in clinical trials of investigational new drugs. Current strategies for scaling either doses of xenobiotics or the dispositional parameters of xenobiotics from animals to man rely on models that take account principally of species differences in weight or body surface area. Interspecies scaling of dispositional parameters such as clearance or volume of distribution commonly involves the comparison of estimates of these parameters for a given xenobiotic among numerous species on the basis of weight with the resultant mathematical relationship used to predict the values of those parameters for that xenobiotic in a species weighing, on average, about 70 kg (i.e., a man). Our approach has been to ascertain whether a useful mathematical model could be developed for predicting the dispositional parameters of a xenobiotic, its half-life and volume of distribution, in humans based exclusively on estimates of those parameters in rats. Based on a data set of about 100 different xenobiotics, we found that values for half-life and volume of distribution of a xenobiotic in humans can be predicted from the estimates of those parameters in rats. *Key words*: half-life, humans, pharmacokinetics, rats, scaling, toxicokinetics, volume of distribution. *Environ Health Perspect* 104:400–407 (1996)

Predicting the dispositional kinetics of xenobiotics in humans from data acquired in animals is an important enterprise. Predicted pharmacokinetic parameters have application in drug development such as in the prediction of initial doses of investigational new drugs for human studies. Predicted toxicokinetic parameters have applications in toxicology such as in the prediction of the time course of exposure after acute or chronic challenge with toxic substances. Knowledge of the time course may be helpful in predicting both the aggressiveness of treatments and the duration of such treatments. Another application is in carcinogenic risk assessment.

Estimates of toxicokinetic parameters in humans for individual xenobiotics may be attained either through interspecies allometric scaling (*1,2*) or through physiologically based pharmacokinetic (PBPK) modeling (*3*), which ultimately must invoke an interspecies scale-up as well, at least for data elicited exclusively from an animal model (*4*). In allometric scaling, kinetic variables such as volume of distribution and half-life are scaled based on the assumption that they are proportional to a power of body weight, and xenobiotic clearance is additionally factored by the species' life span (*5*).

Interspecies scaling as it relates to dosimetry centers on adjustments based on species mass (i.e., body weight), though some prefer that adjustments from one species to another take account of body surface area rather than body weight. For example, the U.S. Environmental Protection Agency suggests that doses be scaled from rats to humans on the basis of the ratio of human body weight to rat body weight (BW) raised to the 0.667 power, as follows (*6*):

$$\text{Dose}_{\text{human}} = \text{Dose}_{\text{rat}} \, (\text{BW}_{\text{human}}/\text{BW}_{\text{rat}})^{0.667} \quad (1)$$

Recent proposals suggest that the exponent used should be 0.75 (*7*) rather than 0.667, and this value appears to be justifiable on the basis that basal metabolic rate is a function of mass raised to the 0.75 power as shown (*8*):

$$\text{Basal metabolism} = a\,M^{0.75} \quad (2)$$

where $a$ is a mass coefficient set at 70 kcal and $M$ is mass in kilograms. Related parameters that scale to $\text{BW}^{0.75}$ include alveolar ventilation, cardiac output, renal clearance, and oxygen consumption (*9*). Most often, the allometric scaling of kinetic variables is undertaken on a case-by-case basis (i.e., xenobiotic by xenobiotic), with kinetic parameters for individual xenobiotics evaluated in each of multiple species (*10*).

We were interested in determining whether reasonable predictions of two kinetic parameters of xenobiotics, volume of distribution and half-life, could be made for humans if one had knowledge of those parameters from rat data only. Our working hypothesis was that a useful predictive mathematical relationship was likely to exist if one regressed known human toxicokinetic variable estimates (volume of distribution and half-life) against known data for the same variables in rats, and did so across a large series of xenobiotics. Such a relationship would establish a single model from which volume of distribution and half-life for any xenobiotic could be predicted for humans and, further, could be predicted entirely from the estimates of those variables in rats.

## Methods

Average values for rats and humans for volumes of distribution of 100 xenobiotics and for half-lives of 103 xenobiotics were obtained from the literature. Most of the xenobiotics were "drugs" insofar as there is a substantially larger literature for human pharmacokinetic parameters than toxicokinetic parameters. A table denoting each xenobiotic, the average toxicokinetic or pharmacokinetic parameters for both rats and humans and the source of the data are given in the appendix.

We modeled half-life and volume of distribution data using the statistical computation program, S-Plus (Mathsoft Inc., Seattle, Washington), which provided confidence limits for model predictions. The program ran on a SPARCserver 10 computer. Our aim was to find a simple yet effective model describing the human data as a function of that of the rat. Further, it was important to identify confidence limits on predictions that may arise from such a model. Noting how the variability in each data set increases linearly with the values for the rat for each parameter we decided to explore logarithmic models because these models are inherently multiplicative in the error terms, as will be seen below.

## Results

After confirming that quadratic terms were not statistically significant, and upon noting that the logarithmic transformations yielded a standard deviation for human values that was constant across rat values (see Figs. 1 and 2), a linear model that is logarithmic in both variables was selected for both data sets:

$$\log(P_{i_{\text{human}}}) = \alpha + [b \times \log(P_{i_{\text{rat}}})] + e_i, \quad i = 1,2,\ldots,n \quad (3)$$

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This work was supported in part by a grant from the Gustavus Pfeifer Foundation.

Received 27 September 1995; accepted 18 December 1995.

where $P$ denotes the kinetic parameter (half-life or volume of distribution) and the errors, $e_i$, are assumed to be normally distributed with a constant standard deviation, σ. This model can be rewritten in more familiar terms as:

$$P_{i_{human}} = a_i \times P_{i_{rat}}^{b} \quad (4)$$

where $a_i$ depends on both the parameter α and the individual errors, $e_i$. Thus, the variability of the actual human parameter value is proportional to the rat value raised to the power $b$.

Results of the regression analysis from S-Plus are given in Table 1. Included are the parameter estimates along with their standard errors for each data set. All the parameters are significant with $p$-values based on the $t$-distribution <0.0001. The $R^2$ values are 0.737 and 0.754 for half-life and volume of distribution analyses, respectively, demonstrating a reasonably good fit in both cases. The estimated regression curves, or prediction lines, for half-life and volume of distribution are shown in Figures 1 and 2, respectively. The exponents ($b$) are 0.83 for half-life and 0.91 for volume of distribution, respectively. Also given in these figures are the 80%, 90%, and 95% prediction intervals for a new human value corresponding to the given rat value. These curves take into account the possible errors in the prediction line itself (in the estimated α and b) and the error inherent to a new observation (as quantified by the regression estimate of σ).

The validity of the regression equations was confirmed as follows: for the half-life data, the regression equation along with the prediction intervals was computed using a subset of the data originally obtained (i.e., all but 18 of the data points ultimately used). The additional 18 data points (these are marked with footnote *a* in the data listings in the appendix) obtained later were compared to the regression results with these points excluded. These points followed basically the same pattern as the larger data set. Furthermore, two of these points fell outside the 80% prediction intervals (about three or four would have been expected to do so); none of these points fell outside the 90% prediction intervals (one or two would have been predicted to do so); and none fell outside the 95% prediction intervals (one or fewer would be expected). As the regression relationship thus proved to be useful in predicting human half-lives from rat half-lives, we concluded that the regression results obtained were valid. Note that the regression results in the tables and figures employ

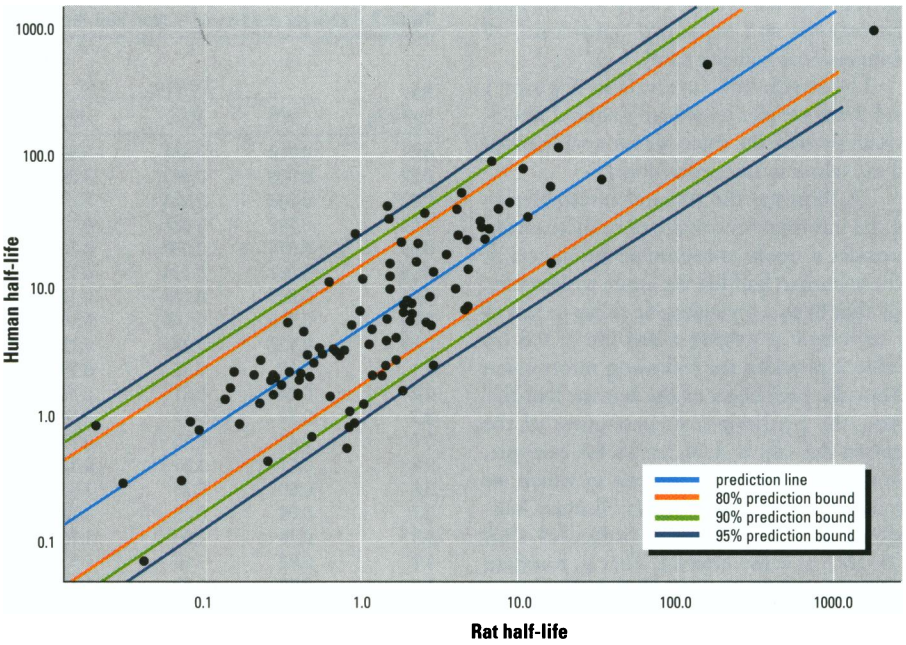


**Figure 1.** Human half-lives for 103 xenobiotics plotted against rat half-lives. Half-lives are given in hours. Both axes are logarithmically scaled.

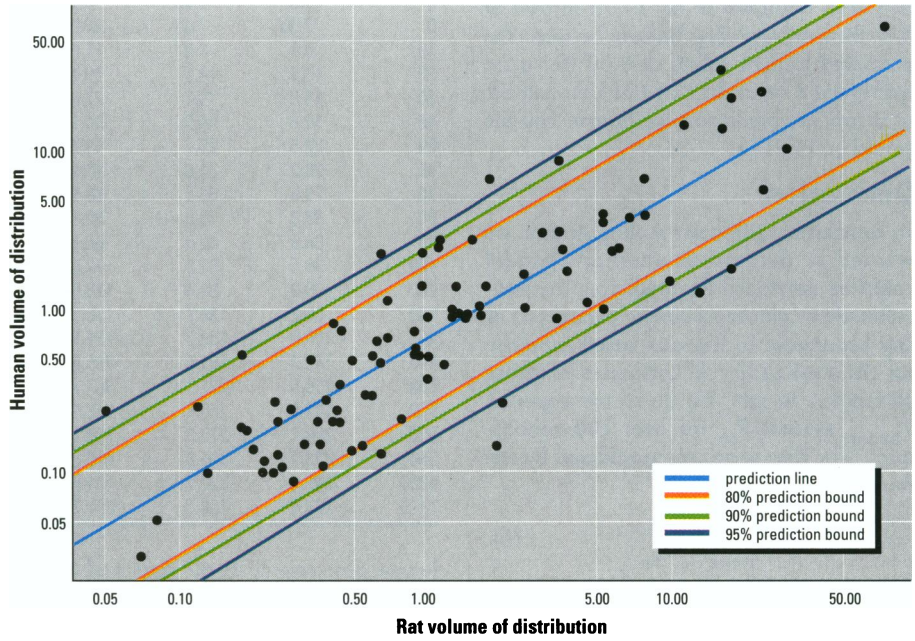


**Figure 2.** Human volumes of distribution for 100 xenobiotics plotted against rat volumes of distribution. Volumes of distribution are given in liters/kilogram. Both axes are logarithmically scaled.

**Table 1.** Regression analysis for human versus rat parameters

| | Estimate | SE | $t$ | $p$ | Residual SE | Multiple $R^2$ |
|---|---|---|---|---|---|---|
| Half-life | | | | | | |
| Intercept (α) | 1.58 | 0.083 | 19.09 | 0.0000 | | |
| Slope ($b$) | 0.83 | 0.041 | 16.83 | 0.0000 | | |
| | | | | | 0.835 | 0.737 |
| Volume | | | | | | |
| Intercept (α) | -0.35 | 0.077 | -4.6 | 0.0000 | | |
| Slope ($b$) | 0.91 | 0.052 | 17.3 | 0.0000 | | |
| | | | | | 0.766 | 0.754 |

the full data set [i.e., the data include both the original and expanded (additional 18 observations) half-life data].

The prediction intervals in Figures 1 and 2 are supplemented by Tables 2 and 3, which present the intervals for a wide range of rat values in numerical form.

To illustrate the use and interpretation of the information contained in these tables, consider a newly encountered substance, *X*, whose human half-life we desire to ascertain. Say that from a toxicokinetic study in rats, *X* is estimated to exhibit a half-life of 0.8 hr. Table 2 provides the following information about the prediction of the human half-life. First, the prediction, or best guess of the human half-life is 4.02 hr. If, for example, we desired to have an interval in which we were 90% confident that the human half-life would lie, Table 3 indicates that 1.0–16.2 hr is the interval. That is, based on the results of this regression analysis, we can be 90% certain that the human half-life for *X* is between 1.0 and 16.2 hr. If interpolation is required, the table is constructed in such a way that linear interpolation should be adequate. For instance, if the rat half-life had been estimated to be 2.7 hr instead of 0.8, then interpolating linearly between the predicted human values of 8.60 (for a rat half-life of 2 hr) and 12.04 (for a rat half-life of 3 hr), the prediction for human half-life would be 11.01 hr.

**Table 2.** Table for predicting human half-life from rat half-life

| Rat half-life | Lower 95% | Lower 90% | Lower 80% | Human half-life estimate | Upper 80% | Upper 90% | Upper 95% |
|---|---|---|---|---|---|---|---|
| 0.01 | 0.019 | 0.025 | 0.034 | 0.106 | 0.327 | 0.451 | 0.598 |
| 0.02 | 0.034 | 0.045 | 0.062 | 0.189 | 0.574 | 0.790 | 1.045 |
| 0.03 | 0.048 | 0.064 | 0.087 | 0.264 | 0.799 | 1.098 | 1.450 |
| 0.04 | 0.062 | 0.081 | 0.111 | 0.335 | 1.011 | 1.387 | 1.830 |
| 0.05 | 0.074 | 0.098 | 0.134 | 0.404 | 1.213 | 1.664 | 2.193 |
| 0.06 | 0.087 | 0.114 | 0.156 | 0.469 | 1.408 | 1.930 | 2.543 |
| 0.07 | 0.099 | 0.130 | 0.178 | 0.533 | 1.598 | 2.189 | 2.882 |
| 0.08 | 0.110 | 0.146 | 0.199 | 0.596 | 1.782 | 2.441 | 3.213 |
| 0.09 | 0.122 | 0.161 | 0.220 | 0.657 | 1.963 | 2.687 | 3.536 |
| 0.1 | 0.13 | 0.18 | 0.24 | 0.72 | 2.14 | 2.93 | 3.85 |
| 0.2 | 0.24 | 0.31 | 0.43 | 1.27 | 3.78 | 5.17 | 6.79 |
| 0.3 | 0.34 | 0.44 | 0.60 | 1.78 | 5.28 | 7.21 | 9.47 |
| 0.4 | 0.43 | 0.56 | 0.77 | 2.26 | 6.70 | 9.14 | 12.00 |
| 0.5 | 0.51 | 0.68 | 0.92 | 2.72 | 8.05 | 10.99 | 14.42 |
| 0.6 | 0.60 | 0.79 | 1.07 | 3.17 | 9.36 | 12.77 | 16.76 |
| 0.7 | 0.68 | 0.89 | 1.22 | 3.60 | 10.63 | 14.51 | 19.04 |
| 0.8 | 0.76 | 1.00 | 1.36 | 4.02 | 11.88 | 16.20 | 21.26 |
| 0.9 | 0.84 | 1.10 | 1.50 | 4.44 | 13.09 | 17.86 | 23.44 |
| 1 | 0.92 | 1.20 | 1.64 | 4.84 | 14.29 | 19.49 | 25.57 |
| 2 | 1.63 | 2.13 | 2.91 | 8.60 | 25.40 | 34.66 | 45.47 |
| 3 | 2.27 | 2.98 | 4.07 | 12.04 | 35.59 | 48.58 | 63.76 |
| 4 | 2.88 | 3.78 | 5.16 | 15.28 | 45.24 | 61.76 | 81.09 |
| 5 | 3.46 | 4.54 | 6.20 | 18.39 | 54.49 | 74.42 | 97.74 |
| 6 | 4.02 | 5.28 | 7.21 | 21.39 | 63.46 | 86.69 | 113.88 |
| 7 | 4.56 | 5.99 | 8.19 | 24.31 | 72.18 | 98.64 | 129.61 |
| 8 | 5.08 | 6.68 | 9.14 | 27.15 | 80.71 | 110.32 | 144.99 |
| 9 | 5.60 | 7.36 | 10.06 | 29.94 | 89.07 | 121.77 | 160.08 |
| 10 | 6.1 | 8.0 | 11.0 | 32.7 | 97.3 | 133.0 | 174.9 |
| 20 | 10.7 | 14.1 | 19.4 | 58.1 | 174.0 | 238.3 | 313.9 |
| 30 | 14.9 | 19.7 | 27.0 | 81.3 | 244.6 | 335.6 | 442.4 |
| 40 | 18.8 | 24.9 | 34.1 | 103.2 | 311.6 | 427.9 | 564.7 |
| 50 | 22.6 | 29.8 | 41.0 | 124.1 | 376.1 | 516.9 | 682.7 |
| 60 | 26.2 | 34.6 | 47.5 | 144.4 | 438.6 | 603.3 | 797.2 |
| 70 | 29.6 | 39.2 | 53.9 | 164.1 | 499.5 | 687.5 | 909.1 |
| 80 | 33.0 | 43.6 | 60.1 | 183.3 | 559.2 | 770.0 | 1018.7 |
| 90 | 36.3 | 48.0 | 66.1 | 202.1 | 617.7 | 851.1 | 1126.4 |
| 100 | 39.5 | 52.3 | 72.0 | 220.6 | 675.2 | 930.8 | 1232.4 |
| 200 | 68.9 | 91.4 | 126.5 | 391.9 | 1214.2 | 1679.5 | 2230.5 |
| 300 | 95.2 | 126.7 | 175.7 | 548.6 | 1712.7 | 2374.3 | 3159.3 |
| 400 | 119.8 | 159.7 | 221.7 | 696.4 | 2186.8 | 3036.7 | 4046.6 |
| 500 | 143.2 | 191.0 | 265.6 | 837.9 | 2643.8 | 3676.1 | 4904.4 |
| 600 | 165.5 | 221.1 | 307.7 | 974.7 | 3087.5 | 4297.9 | 5739.6 |
| 700 | 187.1 | 250.1 | 348.5 | 1107.6 | 3520.5 | 4905.5 | 6556.7 |
| 800 | 208.1 | 278.3 | 388.1 | 1237.3 | 3944.6 | 5501.3 | 7358.6 |
| 900 | 228.5 | 305.8 | 426.8 | 1364.3 | 4361.2 | 6086.9 | 8147.4 |
| 1000 | 248.4 | 332.7 | 464.6 | 1488.9 | 4771.1 | 6663.7 | 8925.0 |
| 1100 | 267.9 | 359.0 | 501.7 | 1611.3 | 5175.1 | 7232.7 | 9692.5 |

## Discussion

In contrast to customary scaling studies, we wanted to determine whether a model could be developed for predicting the toxicokinetic or pharmacokinetic parameters of any xenobiotic in humans based expressly on the availability of estimates of those parameters in rats. To do so we regressed $P_{human}$ against $P_{rat}$ for over 100 xenobiotics. The data were accommodated by the model:

$$P_{i_{human}} = a P_{i_{rat}}^{b} \qquad (5)$$

which, employing the logarithmic transformation, accounts for over 75% of the variance in the relationship between $P_{human}$ and $P_{rat}$. This is particularly striking for a variety of reasons, including, though not limited to, the following: 1) multiple strains of rats were used in assimilating the data sets; 2) some of the data were acquired from male rats and some from female rats; 3) it was assumed, though not necessarily demonstrated, that elimination kinetics in all cases was first order. In fact, some of the xenobiotics exhibited clear dose-dependent kinetics in rats, and when such was the case the kinetic parameters were selected from the lowest dose tested; 4) the sizes and ages of rats used were not uniform; 5) there was insufficient technical detail (e.g., sampling times, duration of sampling, number of subjects) to determine whether all studies from which kinetic data were gathered were structured appropriately (i.e., the goodness of the underlying data cannot be validated); 6) data for each xenobiotic were published generally without regard to chirality considerations; 7) data from a single experiment in a single sample of subjects were taken to be representative; 8) data for humans generally did not take account of sex; 9) no accommodation was made for the differences in protein-binding between species; 10) routes of administration were ignored; 11) elimination pathways were not identical for all xenobiotics in both species; and 12) when explicit weights were not provided, rat weights were set at 0.25 kg and human weights at 70 kg.

Inspection of Tables 2 and 3 shows that the 80% confidence limits for each predicted human parameter embrace an approximate 10-fold range of values. The full range of values for a given parameter for a given xenobiotic when estimated directly even from a single small sample of humans may also extend an order of magnitude or more. It is possible that the range of predicted values could have been tightened, and the scatter of data around the prediction line could have been diminished if

**Table 3.** Table for predicting human volume of distribution from rat volume of distribution

| Rat volume | Lower 95% | Lower 90% | Lower 80% | Human volume estimate | Upper 80% | Upper 90% | Upper 95% |
|---|---|---|---|---|---|---|---|
| 0.01 | 0.002 | 0.003 | 0.004 | 0.011 | 0.031 | 0.041 | 0.054 |
| 0.02 | 0.004 | 0.005 | 0.007 | 0.020 | 0.057 | 0.076 | 0.099 |
| 0.03 | 0.006 | 0.008 | 0.011 | 0.029 | 0.082 | 0.109 | 0.141 |
| 0.04 | 0.008 | 0.010 | 0.014 | 0.038 | 0.105 | 0.141 | 0.182 |
| 0.05 | 0.010 | 0.013 | 0.017 | 0.046 | 0.128 | 0.172 | 0.222 |
| 0.06 | 0.012 | 0.015 | 0.020 | 0.055 | 0.151 | 0.202 | 0.261 |
| 0.07 | 0.013 | 0.017 | 0.023 | 0.063 | 0.174 | 0.232 | 0.299 |
| 0.08 | 0.015 | 0.019 | 0.026 | 0.071 | 0.196 | 0.261 | 0.337 |
| 0.09 | 0.017 | 0.022 | 0.029 | 0.079 | 0.217 | 0.290 | 0.374 |
| 0.1 | 0.019 | 0.024 | 0.032 | 0.087 | 0.239 | 0.319 | 0.411 |
| 0.2 | 0.035 | 0.045 | 0.060 | 0.164 | 0.445 | 0.593 | 0.762 |
| 0.3 | 0.051 | 0.065 | 0.087 | 0.236 | 0.641 | 0.853 | 1.096 |
| 0.4 | 0.066 | 0.085 | 0.113 | 0.307 | 0.831 | 1.105 | 1.419 |
| 0.5 | 0.081 | 0.104 | 0.139 | 0.376 | 1.016 | 1.352 | 1.735 |
| 0.6 | 0.096 | 0.123 | 0.164 | 0.443 | 1.198 | 1.593 | 2.045 |
| 0.7 | 0.111 | 0.142 | 0.189 | 0.510 | 1.377 | 1.832 | 2.350 |
| 0.8 | 0.125 | 0.160 | 0.213 | 0.575 | 1.554 | 2.067 | 2.652 |
| 0.9 | 0.139 | 0.178 | 0.237 | 0.640 | 1.729 | 2.299 | 2.950 |
| 1 | 0.15 | 0.20 | 0.26 | 0.70 | 1.90 | 2.53 | 3.25 |
| 2 | 0.29 | 0.37 | 0.49 | 1.32 | 3.57 | 4.75 | 6.09 |
| 3 | 0.41 | 0.53 | 0.70 | 1.91 | 5.16 | 6.87 | 8.82 |
| 4 | 0.53 | 0.69 | 0.91 | 2.48 | 6.71 | 8.93 | 11.47 |
| 5 | 0.65 | 0.84 | 1.18 | 3.03 | 8.23 | 10.96 | 14.08 |
| 6 | 0.77 | 0.99 | 1.32 | 3.58 | 9.72 | 12.95 | 16.64 |
| 7 | 0.88 | 1.14 | 1.51 | 4.11 | 11.19 | 14.92 | 19.17 |
| 8 | 0.99 | 1.28 | 1.71 | 4.64 | 12.65 | 16.86 | 21.68 |
| 9 | 1.11 | 1.42 | 1.90 | 5.17 | 14.09 | 18.79 | 24.17 |
| 10 | 1.21 | 1.56 | 2.08 | 5.69 | 15.52 | 20.70 | 26.63 |
| 20 | 2.25 | 2.90 | 3.88 | 10.66 | 29.32 | 39.20 | 50.54 |
| 30 | 3.22 | 4.16 | 5.57 | 15.40 | 42.60 | 57.04 | 73.63 |
| 40 | 4.15 | 5.37 | 7.20 | 19.99 | 55.54 | 74.46 | 96.23 |
| 50 | 5.06 | 6.54 | 8.78 | 24.48 | 68.24 | 91.59 | 118.48 |
| 60 | 5.94 | 7.69 | 10.33 | 28.88 | 80.77 | 108.50 | 140.45 |
| 70 | 6.80 | 8.81 | 11.84 | 33.22 | 93.14 | 125.22 | 162.21 |
| 80 | 7.65 | 9.91 | 13.34 | 37.49 | 105.39 | 141.79 | 183.79 |
| 90 | 8.48 | 11.00 | 14.81 | 41.72 | 117.54 | 158.23 | 205.22 |

data sets had been developed prospectively rather than retrospectively and attention had been paid to the itemized points above.

The *sine qua non* for risk assessment purposes appears to be PBPK modeling, which mathematically describes uptake, distribution, metabolism, and excretion of chemicals for physiologically relevant tissue compartments (*11,12*). However, 24 or more physiological, physicochemical, and enzyme kinetic parameters must be known for a given xenobiotic in a given animal model in order for PBPK models to accurately simulate the time course of xenobiotics in tissue compartments. Those active in the field point to the difficulty and expense associated with the development of comprehensive models (*12*).

The simple model presented here allows for the prediction of body burdens of xenobiotics during chronic exposure if the exposure rate is known:

$$\bar{A}_{ss} = E(1.44 \times t_{1/2}) \qquad (6)$$

where $\bar{A}_{ss}$ is the average amount of xenobiotic in the body at steady-state and $E$ is the exposure rate (the fraction of dose absorbed during each exposure period). Alternatively, exposure rates can be estimated from measurement of an average steady-state plasma concentration:

$$E = FD/\tau = \bar{C}_{ss}(V/1.44) \times t_{1/2} \qquad (7)$$

where $D$ is the dose, $F$ is the fraction of the dose absorbed, $V$ is the volume of distribution, $\tau$ is the interval of exposure, and $\bar{C}_{ss}$ is the measured average steady-state concentration of the xenobiotic. To the extent that toxicity or carcinogenicity is a function of reactive metabolites, additional information would be required such as target tissue burdens of such metabolites at steady state. We do not propose that the simple model developed in this paper ought to supplant other strategies incorporated into risk assessment models, be used to predict initial doses of xenobiotics in humans, or be used to gauge the duration of exposures to xenobiotic challenges. Nevertheless, in an era of cost consciousness, it may be useful to apply simple strategies for such purposes when circumstances permit, and it may be instructive to ascertain those circumstances in which simple models may be as usefully informative as far more complex ones.

## Appendix

### Tabulation of Kinetic Parameters in Rats and Humans for 120 Xenobiotics

| Xenobiotic | Volume of distribution (l/kg) Rat | Ref. | Human | Ref. | Half-life (hr) Rat | Ref. | Human | Ref. |
|---|---|---|---|---|---|---|---|---|
| ALO 1567 | 0.45 | (13) | 0.77 | (13) | 15.59 | (13) | 63 | (13) |
| ALO 1576 | 0.97 | (13) | 2.40 | (13) | 33.61 | (13) | 72 | (13) |
| 3TC[a] | | | | | 1.6 | (117) | 2.6 | (117) |
| Aspirin | 0.37 | (14) | 0.15 | (15) | 0.07 | (14) | 0.29 | (15) |
| AZT[a] | 2.12 | (16) | 1.40 | (16) | 0.39 | (16) | 1.35 | (16) |
| CSF[a] | | | | | 1.1 | (118) | 3.5 | (119) |
| FCE 22101 | 0.05 | (17) | 0.24 | (17) | 0.09 | (17) | 0.74 | (17) |
| L-DOPA | 9.8 | (18) | 1.65 | (19) | | | | |
| PCP (phencyclidine) | 23.2 | (20) | 6.20 | (20) | 2.2 | (20) | 16 | (20) |
| MK476[a] | | | | | 1.4 | (120) | 3.8 | (120) |
| Acetaminophen | 1.02 | (21) | 0.95 | (15) | 0.27 | (107) | 2 | (15) |
| Acivicin | 0.65 | (22) | 0.50 | (15) | 1.44 | (22) | 9.5 | (22) |
| Acyclovir | 0.7 | (23) | 0.69 | (15) | 1.39 | (23) | 2.4 | (108) |
| Alteplase | 0.08 | (24) | 0.05 | (15) | 0.04 | (109) | 0.07 | (109) |
| Amiodarone | 72.3 | (25) | 66 | (15) | | | | |
| Amitriptyline | 15.83 | (26) | 15 | (15) | 1.47 | (26) | 15.06 | (15) |
| Amobarbital | 1.46 | (27) | 1.01 | (27) | 1.73 | (27) | 22.7 | (27) |
| Amoxicillin | 0.42 | (28) | 0.21 | (15) | 0.3 | (28) | 1.7 | (15) |
| Amphotericin B | 3.46 | (29) | 3.37 | (15) | 10.2 | (29) | 86 | (125) |
| Antipyrine | 0.92 | (30) | 0.56 | (31) | 1.48 | (28) | 12 | (110) |
| Aprobarbital | | | | | 5.79 | (99) | 24 | (119) |
| Atenolol | 3.41 | (32) | 0.95 | (15) | | | | |
| Baclofen | 1.19 | (33) | 0.48 | (34) | | | | |
| Betamipron | 0.24 | (35) | 0.28 | (35) | 0.16 | (35) | 0.81 | (35) |
| HI-6[a] | | | | | 0.39 | (121) | 1.42 | (121) |
| Brodifacoum[a] | | | | | 156 | (123) | 576 | (122) |
| Caffeine | 0.92 | (36) | 0.61 | (15) | 0.85 | (36) | 4.9 | (15) |

*appendix continued*

*appendix, continued*

| Xenobiotic | Volume of distribution (l/kg) | | | | Half-life (hr) | | | |
|---|---|---|---|---|---|---|---|---|
| | Rat | Ref. | Human | Ref. | Rat | Ref. | Human | Ref. |
| Carbamazepine | 12.91 | (37) | 1.4 | (15) | | | | |
| Cefadroxil | 0.79 | (38) | 0.22 | (15) | 0.82 | (38) | 1.1 | (15) |
| Cefazolin | 0.22 | (39) | 0.12 | (15) | 0.39 | (39) | 1.8 | (15) |
| Cefmetazole | 0.49 | (39) | 0.14 | (39) | 0.14 | (39) | 1.55 | (39) |
| Cefodizime | 0.18 | (40) | 0.19 | (41) | 1.82 | (40) | 1.6 | (41) |
| Cefoperazone | 0.29 | (39) | 0.09 | (15) | 0.15 | (39) | 2.1 | (15) |
| Cefotetan | 0.25 | (39) | 0.13 | (15) | 0.22 | (39) | 2.57 | (15) |
| Cefpiramide | 0.26 | (39) | 0.11 | (39) | 0.32 | (39) | 5.41 | (39) |
| Cefpirome | 0.57 | (42) | 0.31 | (43) | | | | |
| Ceftizoxime | 0.44 | (44) | 0.36 | (15) | 0.26 | (44) | 1.8 | (15) |
| Cephradine | 0.43 | (45) | 0.25 | (15) | 0.81 | (45) | 0.77 | (15) |
| Chlorpromazine | 29.1 | (46) | 11.2 | (46) | 5.55 | (46) | 30 | (15) |
| Cimetidine | 1.36 | (47) | 1.0 | (15) | 0.4 | (111) | 2 | (15) |
| Cisplatin | 2.06 | (48) | 0.28 | (15) | 0.79 | (48) | 0.53 | (15) |
| Clavulanic acid | 0.44 | (49) | 0.21 | (15) | | | | |
| Cocaine | 17.2 | (50) | 2.0 | (15) | 0.85 | (50) | 0.8 | (15) |
| Codeine | 3.6 | (50) | 2.6 | (15) | 0.55 | (124) | 2.9 | (15) |
| Cyclophosphamide | 0.9 | (51) | 0.78 | (15) | 2.49 | (51) | 5.25 | (51) |
| Cyclosporine | 4.54 | (52) | 1.2 | (15) | 15.51 | (52) | 16 | (52) |
| Diazepam | 5.3 | (53) | 1.1 | (15) | 1.42 | (53) | 43 | (15) |
| Dideoxycytidine | | | | | 0.98 | (126) | 1.2 | (127) |
| Diflunisal | 0.13 | (54) | 0.10 | (15) | 1 | (54) | 11.55 | (15) |
| Digoxin | 3.48 | (55) | 9.19 | (15) | 2.5 | (55) | 39 | (15) |
| Enprofylline | 0.34 | (56) | 0.51 | (56) | 0.27 | (56) | 1.42 | (128) |
| Erythropoietin[a] | 0.07 | (57) | 0.03 | (58) | 2.64 | (57) | 5 | (58) |
| Ethanol | 0.61 | (59) | 0.54 | (15) | | | | |
| Ethosuximide | 0.70 | (60) | 0.72 | (15) | 5.5 | (129) | 33 | (130) |
| Ethoxyacetic acid[a] | | | | | 7.2 | (131) | 42 | (131) |
| Etretinate | 1.33 | (61) | 1.50 | (62) | | | | |
| Famotidine | 1.65 | (63) | 1.15 | (15) | 0.44 | (63) | 2.83 | (63) |
| Felbamate | 0.42 | (64) | 0.85 | (65) | 2.78 | (64) | 13.3 | (64) |
| Fentanyl | 11.2 | (66) | 7.7 | (112) | 1.93 | (112) | 7.9 | (112) |
| Fluconazole[a] | | | | | 4 | (132) | 26.4 | (132) |
| Fluoxetine | 15.9 | (67) | 35 | (15) | 3.92 | (67) | 42.1 | (15) |
| Flurbiprofen | 0.36 | (68) | 0.21 | (69) | | | | |
| Gabapentin[a] | | | | | 2 | (133) | 5.5 | (133) |
| Gentamicin | 0.6 | (70) | 0.31 | (15) | | | | |
| Hexobarbital | 0.7 | (27) | 1.2 | (15) | 0.42 | (134) | 4.4 | (134) |
| Ibuprofen | 0.55 | (71) | 0.15 | (15) | 1.31 | (71) | 2 | (15) |
| Imipramine | 17.48 | (72) | 23 | (72) | 3.42 | (113) | 18 | (15) |
| Indomethacin | 0.12 | (73) | 0.26 | (15) | 2.77 | (114) | 2.4 | (15) |
| Isoniazid | 0.63 | (74) | 0.67 | (15) | 0.74 | (74) | 3.1 | (15) |
| Isotretinoin | 1.8 | (75) | 7 | (15) | | | | |
| Ketoconazole | 0.66 | (76) | 2.4 | (15) | 0.53 | (76) | 3.3 | (15) |
| Ketoprofen | 0.37 | (77) | 0.15 | (15) | | | | |
| Ketorolac | 0.38 | (78) | 0.11 | (78) | 1.8 | (78) | 6.5 | (78) |
| Lidocaine | 2.52 | (79) | 1.1 | (15) | 0.62 | (79) | 1.38 | (15) |
| Lithium[a] | | | | | 6.1 | (135) | 28.9 | (135) |
| Meberine[a] | | | | | 0.48 | (136) | 2.5 | (136) |
| Methadone | 7.81 | (82) | 4.24 | (15) | 1.45 | (82) | 35 | (15) |
| Methotrexate | 0.96 | (51) | 0.55 | (15) | 2.66 | (51) | 8.4 | (51) |
| Methylmercury[a] | | | | | 1776 | (137) | 1056 | (138) |
| Methysergide | 1.43 | (80) | 0.93 | (81) | 0.02 | (80) | 0.75 | (81) |
| Metoclopramide | 1.13 | (83) | 2.68 | (15) | 0.33 | (83) | 5 | (15) |
| Metoprolol | 6.72 | (32) | 4.16 | (15) | 0.66 | (115) | 3.2 | (15) |
| Midazolam | 1.64 | (84) | 1.1 | (15) | 0.28 | (84) | 1.9 | (15) |
| Mitomycin C[a] | | | | | 0.47 | (139) | 0.67 | (139) |
| Morphine | 2.87 | (85) | 3.3 | (15) | 0.46 | (116) | 1.9 | (15) |
| Moxalactam | 0.28 | (39) | 0.25 | (15) | 0.34 | (39) | 2.1 | (15) |
| Nicardipine | 1.28 | (86) | 1.1 | (15) | 0.13 | (86) | 1.3 | (15) |
| Nicotine | 5.70 | (87) | 2.6 | (15) | 1.16 | (87) | 2 | (15) |
| Ofloxacin | 1.54 | (88) | 2.95 | (89) | | | | |
| Oxazepam[a] | | | | | 4.5 | (140) | 6.8 | (15) |
| Panipenem | 0.19 | (35) | 0.18 | (35) | | | | |
| Pentamidine[a] | | | | | 0.03 | (141) | 0.28 | (141) |
| Pentazocine | 7.66 | (90) | 7.1 | (15) | 1.13 | (90) | 4.6 | (15) |
| Pentobarbital | 1.64 | (27) | 0.99 | (27) | 2.26 | (27) | 22.3 | (27) |
| Phenobarbital | 1.02 | (27) | 0.54 | (15) | 6.32 | (27) | 99 | (15) |
| Phenprocoumon[a] | | | | | 17.4 | (142) | 128 | (143) |
| Phenylbutazone | 0.24 | (27) | 0.10 | (15) | 4.17 | (27) | 56 | (15) |
| Physostigmine | | | | | 0.25 | (144) | 0.42 | (145) |
| Piroxicam | 1.94 | (91) | 0.15 | (15) | 8.4 | (91) | 48 | (91) |
| Panipenem | | | | | 0.08 | (35) | 0.84 | (35) |
| Prednisolone | 1.74 | (92) | 1.5 | (15) | 0.2 | (93) | 2.2 | (15) |
| Prednisone | 1.3 | (93) | 0.97 | (15) | 0.1 | (93) | 3.11 | (15) |
| Procainamide | 3.72 | (94) | 1.9 | (15) | 0.69 | (94) | 3 | (15) |
| Propafenone | 5.2 | (95) | 3.88 | (95) | 0.97 | (95) | 6.5 | (95) |
| Propranolol | 5.3 | (96) | 4.3 | (15) | 0.72 | (96) | 2.78 | (96) |
| Pyrimethamine | 1.14 | (97) | 2.9 | (15) | | | | |
| Quinidine | 6.0 | (98) | 2.7 | (15) | 2.05 | (98) | 6.2 | (15) |
| Secobarbital | 0.97 | (99) | 1.5 | (100) | 0.89 | (99) | 26.5 | (100) |
| Sertraline | 23 | (101) | 25 | (102) | 4.5 | (101) | 24 | (102) |
| Sulfadiazine | 0.39 | (103) | 0.29 | (15) | 3.86 | (103) | 9.9 | (15) |
| Sulfizoxazole | 0.32 | (103) | 0.15 | (15) | 4.44 | (103) | 6.6 | (15) |
| Theophylline[a] | 0.50 | (79) | 0.50 | (15) | 2 | (146) | 7.3 | (146) |
| Ticarcillin | 0.25 | (49) | 0.21 | (15) | 0.22 | (49) | 1.21 | (15) |
| Tolbutamide | 0.22 | (27) | 0.10 | (15) | 1.82 | (27) | 7.2 | (27) |
| Tolmetin | 0.18 | (104) | 0.54 | (15) | | | | |
| Trimethoprim | 2.47 | (105) | 1.8 | (15) | 0.61 | (105) | 11 | (15) |
| Valproate | 0.66 | (27) | 0.13 | (27) | 4.6 | (27) | 14 | (15) |
| Vancomycin | 1.02 | (106) | 0.39 | (15) | 1.44 | (106) | 5.6 | (15) |
| Verapamil | | | | | 1.6 | (147) | 4 | (15) |
| Warfarin | 0.20 | (27) | 0.14 | (15) | 11.1[b] | (27,148) | 37 | (15) |

[a]Denotes subset of xenobiotics tested against model that had been developed without the subset (see Results).
[b]Unweighted average of mean values reported in Sawada et al. (27) and Takada and Levy (148).

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